

AN INTERDISCIPLINARY PERSPECTIVE ON CURRENT UNDERSTANDING OF
THE PATHOPHYSIOLOGY OF SUBJECTIVE TINNITUS AND BEST CLINICAL
PRACTICES FOR TREATMENT

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ABSTRACT

Subjective tinnitus is commonly experienced, especially by those with hearing loss. It is generally agreed that neural plasticity underlies the pathophysiology of subjective tinnitus. Studies from audiology/hearing research and cognitive neuroscience/neuropsychology are reviewed to illuminate current understanding of the pathophysiology of tinnitus. Research has revealed hyperactivity (increased spontaneous firing rate) in the dorsal cochlear nucleus, inferior colliculus, and other locations in the auditory system. Reduced inhibition related to sensory deprivation at the cochlear level is thought to underlie hyperactivity in auditory structures. Increased neural synchrony is also noted, and may be a correlate of hyperactivity. Reorganization of cortical tonotopic maps is seen in subjective tinnitus, as is reorganization of visual and somatosensory cortical maps with sensory deprivation in those modalities. Non-classical pathways branching from the inferior colliculus and thalamus to the amygdala may be involved in bothersome tinnitus. Providing evidence-based practice for the treatment of subjective tinnitus remains challenging. Current and emerging treatments are reviewed and recommendations for best practice based on research and clinical trial outcomes are discussed.

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Thank you everybody.

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Chapter 1

INTRODUCTION

Tinnitus is the perception of sound in the absence of an external acoustic stimulus. Speech or music that is perceived in the absence of an external stimulus is termed ‘auditory hallucination’ and is distinct from tinnitus. Tinnitus may be divided into two broad categories: objective and subjective. Objective tinnitus is caused by an internal sound which becomes audible, such as turbulent blood flow or muscle contractions. Alternately it may be defined as a sound which is audible to the person and an observer. Subjective tinnitus is the phantom perception of sounds. These sounds are generally characterized as a ringing, roaring, buzzing, hissing, or clicking. Subjective tinnitus is much more common than objective tinnitus. This paper focuses on subjective tinnitus, especially the relationship between cochlear damage (such as due to hearing loss, noise exposure, or ototoxic medication) and tinnitus. Taking into account recent and classical research from audiology/hearing research and cognitive neuroscience disciplines, evidence based clinical practices regarding audiological management of patients with subjective tinnitus will be discussed.

It is estimated that 50 million people experience bothersome tinnitus, with 2.5 million of those people finding it debilitating in their lives (Davis & Rafaie, 2000). The causes of tinnitus and its effective treatment remain nebulous for many patients and clinicians, with patients in many cases unsure of where to turn to for help. As a hearing specialist, an

audiologist is the logical professional to turn to for a patient hearing an obtrusive phantom sound. The scope of practice of an audiologist allows one to “evaluate, diagnose, develop management strategies, and provide treatment and rehabilitation for tinnitus patients” (American Academy of Audiology, 2001). In order for an audiologist to do this, they must take into consideration not only the ears but also the brain. Providing state-of-the-art evidence-based-practice for patients with subjective tinnitus is a challenge and requires a mastery of the current state of knowledge on the subject. In order to best judge potential treatments it is necessary to understand current theories of the pathophysiology of subjective tinnitus as well as clinical trial outcomes for specific treatments or therapies. Understanding current theories and the evidence for them can be helped by considering other scientific disciplines such as cognitive neuroscience.

Audiology and cognitive neuroscience look at subjective tinnitus from two different perspectives. Clinical audiologists wonder how best to prevent, differentiate, diagnose, and treat tinnitus. Hearing researchers wonder what tinnitus tells us about the physiology of the auditory system and how we hear. Cognitive neuroscience researchers wonder how the brain reorganizes when deprived of sensory input, and how this relates to the perception of real and phantom sensations and conscious experience. An interdisciplinary view helps each discipline to create a more complete and useful model of subjective tinnitus, as each provides a different piece of a yet unsolved puzzle.

Evidence for a central cause of subjective tinnitus is shown by studies of VIIIth nerve severance or labyrinthectomy. Patients with tinnitus prior to removal of input from the ear usually still have it afterward, and some who did not have it previously will develop it after the surgery (Andersson, Kinnefors, Elkvall & Anderson, 1997).

Chapter 2

NEURAL PLASTICITY

Neural plasticity is the ability of the nervous system to change, and it happens from development through adulthood. Neural plasticity as reorganization of cortical sensory maps has been shown in adult primates in somatosensory, visual, and auditory modes. Somatotopic representation of skin receptors is clearly organized (representation of adjacent areas on the body is reproduced in the mapping of sensory cortex) and relatively accessible, making it a logical place for studies of cortical plasticity. When sensory input from half of the hand of a monkey was removed by severing the median nerve, an area formerly devoted to that part of the hand in the sensory cortex became innervated by neighboring areas. The result was that the other parts of the hand became more sensitive, as shown by the development of a greater number of smaller receptive fields (stimulus region causing maximal response in a neuron) in those areas. Similar effects occurred when a single digit was amputated in owl monkeys (Kaas, 1991).

In the visual system, retinotopic representation preserves the relationship of neighboring areas in the visual field projected onto the retina. The receptive field for a neuron early in the visual path corresponds to a narrowly defined area in the visual world. It was found that when an area on the retina was lesioned, the size of the receptive fields of adjacent neurons quickly changed. Another interesting discovery was that

although areas in the cortex formerly devoted to the lesioned spot began to process input from neighboring areas; the area corresponding to the lesion remained “silent” in the lateral geniculate nucleus, which is the thalamic relay for visual input (Gilbert & Wiesel, 1990). This phenomenon of cortex showing plasticity (with regard to neighboring areas taking over “abandoned real estate”) but not subcortical areas has been shown in the human central auditory system as well (Langers, van Dijk & Backes, 2005). This has important implications for the relative extent of changes possible at different levels in sensory hierarchies, as well as similarities in sensory representations of different modalities.

Loss of input to neurons promotes plasticity, as the somatosensory and visual studies described above demonstrate. Information about the human perception of the results of plasticity in the wake of stimulus deprivation can be gleaned from cases of phantom limb sensations. Evidence that somatosensory cortex reorganization takes place in humans as in the animal research is shown in the case studies of amputees made by Vilayanur Ramachandran. In somatosensory cortex, representation of the face lies next to representation of the hand and forearm, as shown in Figure 1. One young man who had recently had his forearm amputated reported feeling his phantom hand being stroked when a Q-tip was lightly brushed across his face. This “face-hand” was well defined and stable over successive trials. Ramachandran reports that 3 of 7 forearm amputees showed a similar phenomenon (Ramachandran, 1993). He has reported similar experiences for lower limb amputations and sexual stimulation, with one amputee reporting a magnification of orgasm experienced in his phantom foot (in the somatosensory map, the region corresponding to genital stimulation lies below that for the foot, see Figure 1).

Although demonstrating evidence for perceptual correlates of somatotopic cortical reorganization, the complex nature of hearing loss in the auditory periphery is very different from amputation and may make generalization from “phantom limbs” to “phantom sounds” untenable, except perhaps for cases of cochlear ablation or severing of the VIIIth nerve. However, it does show that animal model experiments are relevant to human experience and lends insight into human conscious perception of phantom phenomena. Central neuropathic pain (pain that occurs in the absence of pain receptor stimulation) and tinnitus are considered more similar, and highly analogous (Møller 2007a)

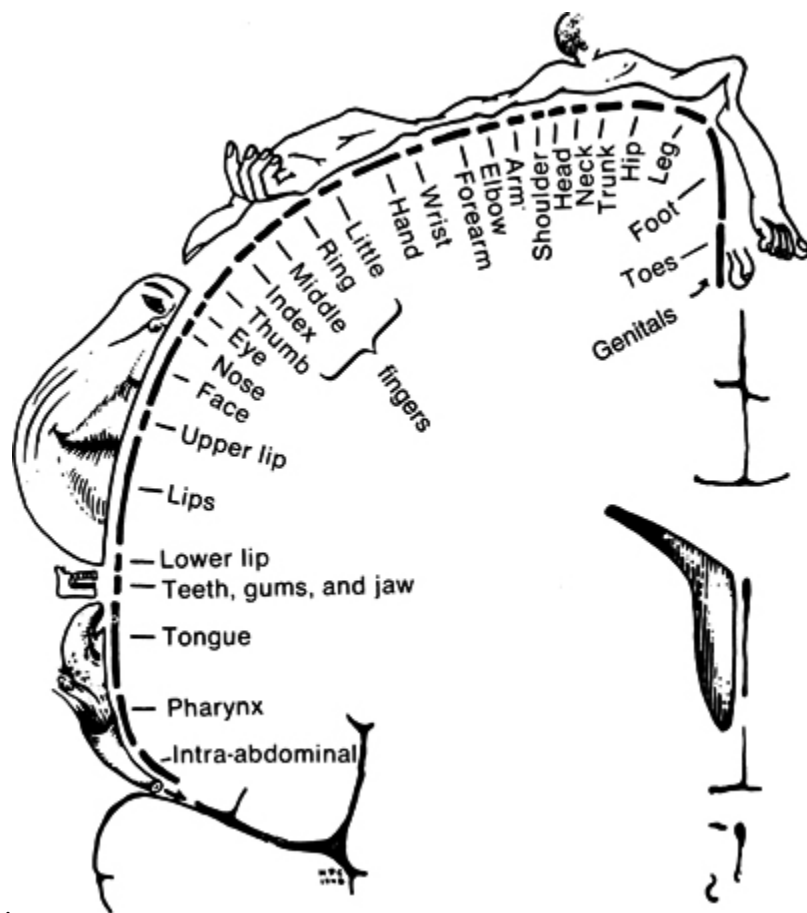


Fig. 1.1: The Penfield homunculus showing mapping of inputs to primary somatosensory cortex. From Ramachandran (1993).

In a demonstration of a differently motivated cortical change, owl monkeys taught a tone discrimination task for tones around 2.5 kHz showed increased cortical representation of those frequencies in primary auditory cortex compared to controls (Recanzone, Schreiner & Merzenich, 1993). Similar results have been shown via magnetoencephalography (MEG) in somatosensory representation of fingers of violinists' plucking (left) hands and via functional magnetic resonance imaging (fMRI) in non-musician adults trained in a finger manipulation task where subjects were taught to touch their thumb to different fingers on the same hand in a specified order (Elbert, Pantev, Wienbruch, Rockstroh & Taub, 1995; Karni et al., 1995). Auditory discrimination therapy (ADT) is designed to change cortical representation of frequencies using a similar task so that areas for over-represented tones which may be responsible for tinnitus perceptions are diminished while area for "trained" frequencies is increased (Herraiz, Diges & Cobo, 2007). The correlation between perceived tinnitus pitch and input-deprived frequency representation in auditory cortex is not understood well enough to precisely determine the training frequencies, and research is underway to determine the optimal training frequencies for a given tinnitus pitch. These types of therapies, rooted in current theories of neuroplasticity, show promise and may evolve to become powerful tools that help audiologists to treat tinnitus patients.

NEURAL PLASTICITY AND THE AUDITORY SYSTEM

Neural plasticity can be effected through changes at the level of the synapse, creation or elimination of synapses, dendritic sprouting or pruning, and axon growth or death (Møller, 2007b). Neural plasticity has been revealed in cortical and subcortical levels of

the auditory system, primarily in the dorsal cochlear nucleus, inferior colliculus, and auditory cortex. Plastic changes commonly reported are hyperactivity (rise in spontaneous neural firing rate) and increased synchrony in neural firing and reorganization of cortical tonotopic maps. Other reorganization may involve redirection of information to neighboring, non-auditory areas of the brain, such as the limbic system, and strengthening of the extralemniscal (non-classical) pathways.

The dorsal cochlear nucleus (DCN) is directly innervated by the ipsilateral auditory nerve (as is the ventral cochlear nucleus); a loss of stimulation due to a damaged cochlea first affects this structure. This is the lowest level in the auditory system where hyperactivity related to tinnitus has been found, and both hyperactivity in the DCN and tinnitus have been shown to develop following outer hair cell injury in the cochlea and to persist following severing the VIIIth nerve (Kaltenbach, Zhang & Finlayson, 2005). Changes in pitch and loudness in tinnitus over time are correlated with changes in magnitude and frequency location in tonotopic organization of hyperactivity in the DCN (Kaltenbach, Zhang & Afman, 2000). This higher spontaneous firing rate can be attributed to a reduction in inhibition related to loss of input at the cochlear level, and is shown in animal studies of several species whether the cochlear damage is due to hearing loss caused by noise or ototoxic substances.

Above the level of the DCN, multiple parallel pathways ascend and all ascending auditory pathways converge onto the inferior colliculus, which receives information from both ears. The inferior colliculus (IC) neurons project to the medial geniculate nucleus of the thalamus, and also to other areas such as the superior colliculus where auditory and

visual information is integrated, and the cerebellum. Tinnitus related changes (increased spontaneous firing rate and increased neural synchrony) have been widely documented in the IC. A study in the chinchilla showed identical changes in a subpopulation of neurons in the IC whether cochlear trauma was due noise damage causing sparse inner hair cell (IHC) and sparse outer hair cell (OHC) loss, cisplatin causing mostly OHC loss with sparse IHC loss, or carboplatin causing pronounced IHC loss and no OHC loss (Bauer et al., 2008). All three groups showed behavioral psychophysical evidence of chronic tinnitus resembling a 1000 Hz tone following cochlear damage. In all three groups the largest change compared to controls was a subpopulation of neurons distributed throughout the IC that showed three characteristic features. A multidimensional analysis of multiple single unit recordings of the spontaneous activity showed high bursting (hyperexcitability), low interspike interval variance (increased synchrony), and within-burst peak spiking of approximately 1000 per second. This study concluded that the same underlying correlates of tinnitus appeared regardless of the type of cochlear trauma, and identified changes that occurred in all three groups.

Reorganization in auditory cortex is the third correlate of subjective tinnitus. In humans, this is largely explored via MEG and shows that neurons in primary auditory cortex that are deprived of input become sensitive to frequencies neighboring those that were lost. Frequencies neighboring the area of lost input become larger, while areas corresponding to lost frequencies shrink resulting in a distorted cortical tonotopic map (Eggermont, 2007). Changes in cortical maps are correlated with perceived strength of tinnitus rather than peripheral hearing loss and appear to have much in common with

somatosensory cortical map changes and phantom limb sensations (Muhlnickel, Elbert, Taub & Flor, 1998).

Some people with subjective tinnitus find the tinnitus particularly bothersome or even debilitating, while others do not. One theory that attempts to explain why this happens involves reorganization, not just in the auditory system, but in other regions as well.

Auditory information ascends from ear to cortex via two pathways, the classical/lemniscal pathway and the non-classical/extralemniscal pathway. The non-classical pathway projects from the external nucleus and dorsal cortex of the IC to the dorsal and medial thalamic nuclei, and responds to more than auditory stimuli (multi-modal). Dorsal and medial thalamic nuclei are implicated in neuropathic pain as well as some forms of severe tinnitus (Møller, 2007a). The multi-modal nature of this pathway may explain why many forms of tinnitus involve a tinnitus perception that changes with somatic manipulation such as neck tension or eye movement, and why tinnitus is associated with temporomandibular joint (TMJ) problems. From the dorsal and medial thalamic nuclei the pathway continues to the auditory association cortex, bypassing the primary auditory cortex. There is also a subcortical connection from the dorsal thalamus to the lateral nucleus of the amygdala. The amygdala is located in the medial temporal lobe by the hippocampus and is implicated in implicit fear/aversive conditioning. It receives sensory information from two pathways, the subcortical pathway just described (the “Low Route”) and a second pathway which goes from the thalamus to primary sensory cortex and then to the amygdala (the “High Route”, see Figure 2). This allows threat analysis to be both fast and sure, with the subcortical pathway being the fast one. The amygdala mediates unconscious emotional response to aversive stimuli and also

interacts with memory systems to enhance memory for aversive emotional events, real or imagined. It may be that a peripheral hearing loss leads to a lessening of inhibition resulting in high spontaneous firing rates in auditory pathways including the non-classical pathway leading to involvement of the amygdale and labeling of the percept of tinnitus as aversive.

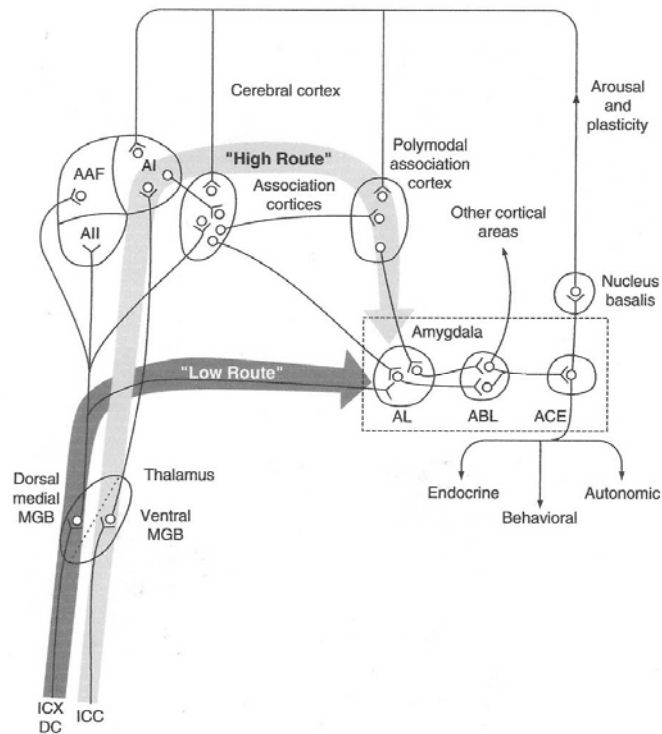


Fig. 1.2: Illustration of the “High Route” and “Low Route” of sensory information to the lateral nucleus of the amygdale. AL: lateral nucleus of the amygdala; ABL: basolateral nucleus of the amygdala; ACE: central nucleus of the amygdala; MGB: medial geniculate body; AI: primary auditory cortex, AII: association auditory cortex. From Møller (2007) after LeDoux (1992).

Chapter 3

CURRENT AND EMERGING TINNITUS TREATMENTS

There are many potential avenues of treatment for tinnitus. Pharmaceuticals (and herbal remedies, minerals, vitamins, etc.), electric/magnetic stimulation, hearing aids, cochlear implants, maskers/sound therapy, cognitive behavioral therapy/extinction training, neurofeedback, tinnitus retraining therapy, tinnitus activities therapy, auditory discrimination therapy, neuromonics treatment, and object identification and attention training have all been used with varying success. Currently, there is no “magic bullet” treatment which will definitely help any given patient with tinnitus, and no treatment permanently removes the tinnitus percept. Problems for clinicians include: poorly understood pathophysiology of tinnitus, lack of diagnostic methods to clearly divide patients into clinically relevant subgroups, lack of gold-standard clinical trials, lack of pre-clinical trials to potentially introduce new and effective treatments, and lack of standardization of outcome measures to compare research and clinical trial outcomes. Despite these problems, recent breakthroughs in tinnitus research show promise for refinement of existing treatments and development of new ones.

PHARMACEUTICAL TREATMENTS

Pharmaceutical treatments for tinnitus may be delivered systemically (usually orally) or via intratympanic injection. There are many drugs that have been administered in an attempt to provide tinnitus relief, but many (even the most commonly administered) lack formal clinical trials. Optimally, a clinical trial is randomized, placebo-controlled, and

double blinded (RCTdouble). This means that the subjects are randomly assigned to treatment groups, one of the groups is given a placebo treatment, and the investigator and subjects are unaware of which groups are which from the beginning to the end of the study. This prevents allocation bias by the investigator (“cherry picking” subjects for certain treatment groups) and bias in assessment of outcomes by the investigator and subjects (allowing knowledge of whether the subject received placebo or treatment to bias reporting of effects of the treatment). Some clinical trials are randomized, placebo-controlled, and single-blinded (RCTsingle); in these trials the subjects do not know which group they have been assigned to but the investigator does. The problem of subgroups of tinnitus types emerges to cloud reporting of results in clinical trials. It may be that a given drug treatment is very effective for a certain subpopulation of tinnitus subjects, but if this subgroup is not isolated for study the treatment may fail to show significant efficacy or show reduced efficacy. Currently there are not standard subgroupings of subjective tinnitus types, partially due to the poorly understood physiology of the phenomenon, but some that have been suggested are Meniere’s related tinnitus and tinnitus that can be physically modulated (changes when body or eye position is varied, or when the skin is stimulated). This is because the tinnitus reported for Meniere’s patients is fairly unique, and is one of three symptoms that defines the disease. It is hypothesized that tinnitus that changes in combination with somatosensory modulation may involve maladaptive changes in the non-classical auditory pathways and related areas. Another postulated subgroup would divide subjective tinnitus patients according to whether the tinnitus is unilateral (heard in one ear) or either central or bilateral (heard

in both ears or in the head) as there is some evidence that these are different types of tinnitus (Ochi, Ohashi & Kenmoshi, 2003).

Dexamethasone as a treatment for tinnitus in patients with unilateral Meniere's disease has been investigated with a RCTdouble study, which found that tinnitus was relieved for 48% of the patients when the steroid was delivered intratympanically (Garduno-Anaya, Couthino De Toledo, Hinojosa-Gonzalez, Pane-Pianese & Rios-Castaneda, 2005). Investigation of other steroids such as methylprednisolone (often used to treat sudden sensorineural hearing loss) have shown no significant effect compared to placebo (Slattery, Fisher, Iqbal, Friedman & Liu, 2005). Diuretics are often used in Meniere's treatment, but there is no clear evidence that they alleviate tinnitus.

Lidocaine is a local anesthetic and has been investigated in tinnitus treatment for many years. Although many studies show that lidocaine can temporarily alleviate tinnitus, the effect is short-lived and there are no high quality clinical trials that might justify clinical use.

Benzodiazepines are GABA_A receptor agonists. GABA-aminobutyric acid (GABA) is an inhibitory transmitter that may be implicated in reduction of inhibition resulting in the hyperactivity in auditory system structures now commonly recognized as a correlate of subjective tinnitus (Eggermont, 2007). Some studies have shown reversal of signs of hyperactivity in the DCN and IC in animal models (Szczepaniak & Møller, 1995), but there is no clinical evidence for efficacy. Benzodiazepine use has negative side effects such as a high potential for dependence and sedation. There is insufficient evidence to support the use of more modern anti-depressants such as SSRIs (selective

serotonin reuptake inhibitor/serotonin-specific reuptake inhibitor) for the treatment of tinnitus, although a patient who is exhibiting potential signs of depression related to the tinnitus should be referred to a psychiatrist. Anti-depressants have been shown to be helpful for tinnitus patients who are depressed (Robinson, 2007).

Anti-convulsant drugs have been investigated as a potential tool in tinnitus treatment. Most have unfortunate side effects at the dosages used to treat epilepsy, but have been explored at lower dosages in tinnitus treatment. No studies in humans have as yet showed promise, although an animal model study showed carbamazepine to protect against tinnitus in a dose dependent fashion in rats with salicylate induced tinnitus (Darlington & Smith, 2007). A RCTdouble showed gabapentin to have no significant effect on severity of tinnitus (Witsell, Hannley, Stinnet & Tucci, 2007). The anti-spasticity drug baclofen was found to cause withdrawal symptoms in some of the subjects but to be no better than placebo at reducing tinnitus (Darlington & Smith, 2007).

Acamprosate is a drug used to treat alcohol dependence. It acts by increasing GABA and decreasing glutamate (an excitatory neurotransmitter) at NMDA receptors which is thought to decrease the hyperactivity seen in tinnitus. It was shown in a RCTsingle study to be effective in relieving tinnitus (though not completely removing any tinnitus sensations except in 3 of 50 subjects) significantly compared to placebo, with 86.9% of subjects in the acamprosate group reporting lessening of tinnitus sensation, and 47.8% of those subjects reporting continued effects at 90 days post drug administration (Azevedo & Figueiredo, 2007). Further clinical trials may reveal this drug to be of help in treating tinnitus.

Many herbal remedies (such as ginkgo biloba), vitamin and mineral supplements, and antioxidants are marketed as tinnitus treatments. A review of the literature fails to show any scientific or clinical support for these substances (Enrico, Sirca & Mereu, 2007). Because these substances may be taken in combination with other pharmaceuticals or at very high dosages by patients who consider them harmless, it is important to determine whether tinnitus patients are self medicating and whether their physician has cleared them to use these substances at the levels they are being used and in conjunction with any other medications they may be taking. Patients do not need to be dissuaded from trying these alternative remedies (as long as there are no contraindications), as they may receive real benefit from the placebo effect.

In the future, as an effective pharmaceutical treatment continues to be sought, newer animal model methods which allow assessment of behavioral evidence of the percept of tinnitus can be used to screen new substances for pre-clinical trials. These methods have not been exploited to the extent that they could be, but offer a cost effective way to screen many potential tinnitus reducing drugs prior to costly clinical trials, and hopefully audiologists will see more in the literature when keeping up with tinnitus research. Currently, there is little evidence to support the use of drug treatment by professionals involved in treating tinnitus, although new animal methods used in discovering new drugs and further trials on those drugs (and some that currently show promise) may change that.

SOUND THERAPIES

Sound therapies for tinnitus include hearing aids which supply appropriately amplified sound stimulation in the region of the hearing loss whenever sound in that frequency region is present in the environment, maskers which supply a constant sound and are worn as an ear-level device, and other sound generators which may be ear or table level and may provide broadband or narrowband noise, pre-recorded environmental sounds (such as the seashore or water running), or pleasant music. Sound therapies are appropriate for tinnitus patients whether the tinnitus is bothersome or merely noticeable. As previously mentioned with Auditory Discrimination Therapy, there is not a simple correlation with attenuation of tinnitus and tinnitus pitch, and efforts to maximize masking of tinnitus with a similar pitch have been unsuccessful (M. Jastreboff, 2007). Sound therapy is an important area of knowledge for audiologists, especially as tinnitus and hearing loss are highly correlated and tend to co-occur (Sindhusake et al., 2003). Studies examining the effects of hearing aid use on tinnitus are often outdated, and cannot be compared to today's nonlinear digital options for amplification (Del Bo & Ambrosetti, 2007). One recent study showed significant tinnitus reduction for hearing aid or sound therapy users, with the added benefit for hearing aid users of improved hearing and communication (Folmer & Carroll, 2006). Overall there is a need for high quality research to assist audiologists in providing evidence-based-practice in this important area, particularly in areas pertaining to programming the hearing aids. It is not clear whether turning off noise reduction or increasing gain in frequencies corresponding to tinnitus perception would be helpful. How best to use new hearing aid technologies such as the Zen program in the Widex Mind 330 and 440 hearing aids should be

understood by audiologists treating tinnitus. What we know about neural plasticity and effects of sensory deprivation further justify use of amplification for hearing loss. Hearing aids alone do not appear to be enough to significantly help patients with bothersome tinnitus as a primary complaint, but it is possible that hearing aids may act as a preventive measure for developing tinnitus, and possibly protect against non-bothersome tinnitus becoming bothersome. Additional research in this area would be illuminating. As in many other areas of treatment, a diagnostic tool that categorizes patients in a clinically relevant manner and provides a standardized measure of treatment outcome would be most welcome.

COUNSELING THERAPIES

Cognitive behavioral therapy is a short term course of therapy using cognitive restructuring of thoughts, relaxation, and controlled exposure to exacerbating symptoms to promote habituation. No evidence shows clinically significant improvement when used in isolation, but it is often combined with other treatments (sound therapy or pharmaceutical treatment) with varying degrees of success (Martinez-Devesa, Waddell, Perera & Theodoulou, 2009). Informational/educational counseling is included in treating patients with non-bothersome or bothersome tinnitus and it is considered essential just as it is when treating a patient with a hearing loss, but is not intended as a treatment for tinnitus per se.

MULTI-MODAL TREATMENTS

Tinnitus retraining therapy (TRT) is a clinical method for treating bothersome tinnitus based on a neurophysiological model similar to what is described in this paper (P. Jastreboff, 2007). TRT uses a combination of counseling and sound therapy to recategorize the tinnitus stimulus as neutral rather than aversive, separate the concepts of the tinnitus sensation and distress, and allows the presence of the sound of tinnitus while reducing tinnitus related distress. This method attempts to enable a tinnitus patient to habituate to the tinnitus sensation. Habituation refers to learning to ignore a stimulus that has no meaning. Most tinnitus patients, who experience tinnitus that is noticeable but not usually bothersome, are able to habituate to their tinnitus. Jastreboff postulates three stages in the development of tinnitus, with a fourth stage taking place in bothersome tinnitus: generation of abnormal neural activity that causes the percept of the tinnitus, interpretation of the abnormal neural activity, and evaluation at higher central nervous system centers. In bothersome tinnitus, there is sustained activity in non-auditory regions such as the limbic (emotional) system and sympathetic autonomic nervous system which causes the tinnitus to be evaluated as a negative stimulus (see Figure 3). Coincidental classical conditioning is thought to play a role in the development of bothersome tinnitus, for example when a person is in a negative emotional state when they notice the tinnitus. Classical conditioning pertains to association of a stimulus that evokes a measurable response (the unconditioned stimulus, such as distress due to a negative emotional state) with a stimulus that does not (the conditioned stimulus, such as early tinnitus). Paired presentation of the stimuli results in the measurable response to the unconditioned stimulus occurring upon presentation of the conditioned stimulus alone (tinnitus

perception alone is enough to evoke distress). This model provides an explanation for why the non-classical pathway branch to the amygdala might become significantly active in bothersome tinnitus, and it offers a possible solution: just as conditioning sharpened negative response to tinnitus, conditioning can facilitate habituation to the tinnitus. TRT utilizes counseling to help the patient re-categorize tinnitus as a neutral stimulus, and sound therapy to decrease the abnormal neural activity associated with the tinnitus. Many studies, including an independent randomized study, show TRT to be highly effective at alleviating the impact of tinnitus in patients with bothersome tinnitus (P. Jastreboff, 2007). It is a treatment that requires a significant dedication of time and resources on the part of the clinician, and results, while long lasting, require months to years of treatment.

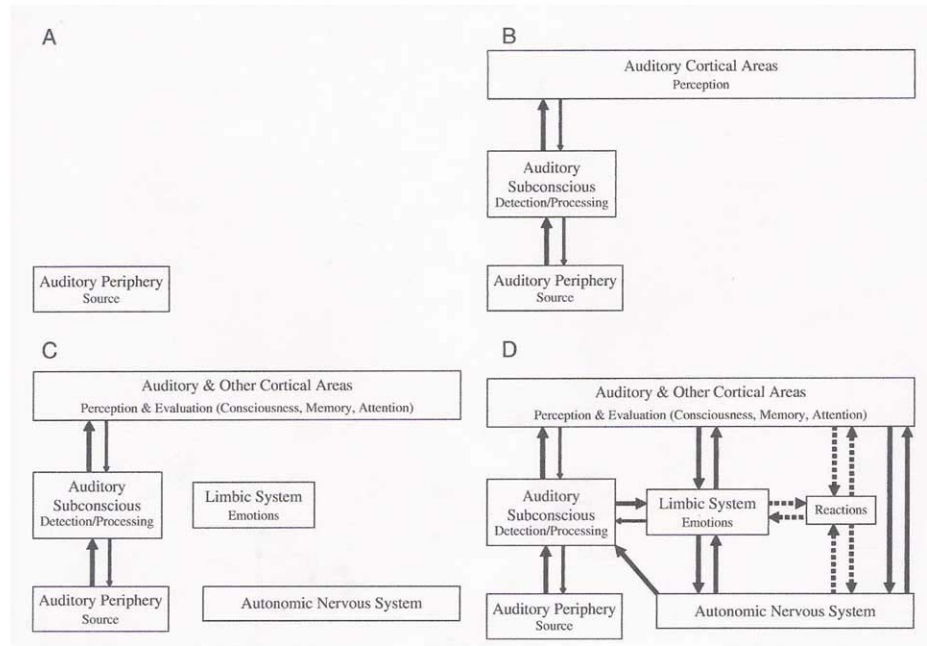


Fig. 2.1: Jastreboff tinnitus model. A: first stage of tinnitus, peripheral disruption in normal function; B: abnormal neural activity perception; C: evaluation of tinnitus as a neutral stimulus in non-bothersome tinnitus (no involvement of limbic and autonomic system); D: bothersome tinnitus showing self-strengthening loops of neural activity involving higher level evaluative systems, the limbic system, and the autonomic system. From Jastreboff (2007).

Neuromonics Tinnitus Treatment combines use of a relaxing musical sound therapy that is tailored to the patient's hearing loss (if applicable) and counseling and support in a two stage program of desensitization to bothersome tinnitus. Neuromonics sound therapy is designed to interact with the tinnitus and the limbic system by allowing intermittent perception of tinnitus within a pleasant and relaxing music therapy. Candidacy for this treatment is designed to allow a subgroup of patients with bothersome tinnitus who are likely to have a successful outcome. This therapy is not appropriate for those with a 4 frequency pure tone average greater than 50 dB HL in the better hearing ear, a level of tinnitus disturbance not clinically significant, or co-morbid issues such as cognitive impairment or psychosis too great to allow the ability to reliably perform test measures (Davis, Paki & Hanley, 2007). The desired outcome of Neuromonics treatment is a rapid and profound decrease in severity of tinnitus and improvement in quality of life. The third round of clinical trials demonstrated that 91% of the subjects in the Neuromonics test group showed significantly reduced tinnitus impairment as measured on the Tinnitus Reaction Questionnaire (TRQ) within 6 months of treatment, with 80% reporting scores that were no longer clinically significant (Davis et al., 2007). Neuromonics incorporates many of the tenets of TRT, such as the physiological model, but takes less time and clinical resources to produce very impressive results for a subpopulation of patients who experience bothersome tinnitus.

OTHER TREATMENTS

Transcranial Magnetic Stimulation (TMS) is a noninvasive method that causes global excitement of a population of neurons in the brain. Repetitive TMS (rTMS) refers to repeated treatments and can produce longer lasting changes. Currently it has been shown that TMS or rTMS can temporarily interrupt tinnitus perception (much like lidocaine) but that the effects are transitory (Kleinjung, Steffens, Londero & Langguth, 2007).

Implanted electrodes in auditory cortex have been shown to be effective for some subjects with tinnitus but not a majority (De Ridder, De Mulder, Menovsky, Sunaert & Kovacs 2007), although this might be an area where a significant effect might be found for a subgroup of tinnitus patients with severe unilateral tinnitus. Trans-electrical nerve stimulation (TENS) is a treatment sometimes successful for patients with neuropathic pain, and may show promise for patients with somatic-modifiable tinnitus, although reduction of tinnitus was only shown in 46% of patients chosen for the study due to suspected somatic-modifiable tinnitus (Herraiz, Toledano & Diges, 2007).

Auditory Discrimination Therapy (ADT) is mentioned in the introduction of this paper, and is designed to change cortical representation of frequencies using a similar task so that areas for over-represented tones which may be responsible for tinnitus perceptions are diminished while area for “trained” frequencies is increased. Results of a controlled study showed that 40% of the subjects showed some tinnitus improvement (Herraiz, Diges & Cobo, 2007), where subjects included showed a tinnitus handicap in the mild to moderate range on the Tinnitus Handicap Inventory (THI). It remains to be

seen whether a different protocol will yield more promising results for this tinnitus intervention.

Another training therapy for tinnitus is being developed to augment counseling and sound therapy via a take-home auditory training program using a stimulus-drill approach. Object identification and attention training is designed to improve the ability to attend to relevant sounds while ignoring distractors by encouraging adaptive plasticity related changes in the ability to attend to real sounds while ignoring tinnitus percepts using Auditory Object Identification and Localization (AOIL) tasks (Searchfield, Morrison & Wise, 2007). Only a small (n of 10) pilot study has been completed at this time, with results showing a reduction in minimal masking levels. More research will be necessary to evaluate AOIL for clinical use.

New neurofeedback paradigms based on MEG research on tinnitus in humans are showing some promising results. MEG measures the magnetic fields produced by electrical activity in the brain and reflect the synchronous activity of large populations of neurons. It is somewhat similar to electroencephalography (EEG) (which measures electric fields at the scalp produced by electrical activity in the brain) but boasts a slightly better spatial resolution while preserving excellent temporal resolution. Differences in MEG recordings from temporal regions in tinnitus patients compared to controls show characteristic changes which may be due to increased neural synchrony in the auditory system in tinnitus. Specifically, slow waves in the delta range (0.5-4 Hz) are increased while alpha activity (8-12 Hz) is reduced (Dohrmann, Weisz, Schlee, Harmann & Ebert, 2007). Using (relatively inexpensive compared to MEG) EEG equipment, 21 subjects

with chronic but not severe tinnitus underwent a neurofeedback training program of ten 30 minute sessions over four weeks. Subjects who were able to learn to control their brainwaves showed a significant reduction in tinnitus. One patient, who was particularly good at the neurofeedback training was able to achieve complete tinnitus relief. Subjects who were unable to do the training did not benefit from the treatment while those who were able to modify both bands simultaneously showed an average tinnitus intensity reduction of 71% (Dohrmann et al., 2007). Based on the results of this study, the emerging field of neurofeedback treatment is worth keeping an eye on, although there are no clinical trials at this time.

Chapter 4

CONCLUSION

Providing state-of-the-art evidence-based-practice for subjective tinnitus is extremely challenging. Although progress is being made, the pathophysiology of tinnitus is still poorly understood. Many treatments lack evidence on which to base their use, especially pharmaceutical treatments. It is unclear how best to divide tinnitus into clinically relevant subgroups, although it is generally agreed that this would be beneficial. Consistency in assessing patients and in measuring treatment outcomes is an urgent need in the field, and agreement on outcome measurements would greatly facilitate comparison across research and treatment studies. Relevant animal models involving behavioral methods to assess tinnitus perception in animal subjects are underused, but show great promise for advancing our understanding of tinnitus and discovering potential drug treatments.

Recommendations for clinical treatment begin with keeping up to date on results of clinical trials or studies addressing clinical efficacy of new or existing treatments. Audiologists should be knowledgeable about developments in our understanding of the pathophysiology of tinnitus. Audiologists should make external referrals to appropriate professionals when necessary. Physician referrals ensure the patient is evaluated to rule out any treatable disease that may cause or contribute to tinnitus and check that any self-medicating the patient is doing is not potentially harmful. A psychiatrist can assess whether clinical anxiety or depression are present and prescribe psychoactive medication when appropriate. Audiological evaluation should be performed to assess hearing loss. Other test measures such as tinnitus pitch matching, tinnitus loudness levels, minimal

masking levels, etc. may be used to characterize a patient's tinnitus or as part of a treatment (as in Neuromonics). Hearing aids should be used to treat hearing loss, as this minimizes sensory deprivation at the periphery. External sound sources may be beneficial for patients whose tinnitus is intermittently bothersome or distracting. An evidence based (valid and reliable) tool such as the Tinnitus Reaction Questionnaire should be used to verify whether tinnitus is bothersome to the patient (and to what degree). Luckily, there are evidence-based treatments for bothersome tinnitus that have been shown to be effective at reducing tinnitus distress. TRT or Neuromonics are indicated for such patients.

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